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UNDERSTANDING THE DISEASE

Intrathoracic effects of PEEP: beyond oxygenation

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In patients with acute respiratory distress syndrome (ARDS), positive end-expiratory pressure (PEEP) is fundamental to correct hypoxemia by re-aerating the lungs, and became a cornerstone of mechanical ventilation across many indications. However, it was soon realized that oxygenation is not a reliable marker of benefit because decreasing the cardiac output with PEEP also reduces shunt, leading to higher PaO_2 while global oxygen delivery actually decreases. Understanding PEEP's effect beyond gas exchange is crucial: PEEP affects lung mechanics, counteracts chest wall influence in obesity, maintains airway patency, and influences end-organ function through its hemodynamic effects on venous return, right ventricle afterload and cardiac output, and organ perfusion. Here, we summarize intra-thoracic physiological mechanisms and their implications.

Lung volume: balancing recruitment and overdistention

In ARDS, lung volume decreases due to alveolar injury, flooding, and gravitational collapse of dependent regions, while non-dependent regions remain aerated (Fig. 1a, b). The result is the "baby lung", a functionally small yet relatively healthy portion of the lung, comprising the non-dependent regions subjected to the full tidal volume, potentially propagating injury [1]. PEEP aims to reopen previously collapsed regions (or keep them open), thereby increasing baby lung size and minimizing lung injury progression. However, it also inflates open alveoli, promoting overdistention and injury to the baby lung itself. Given the heterogeneous nature of lung abnormalities, a single PEEP level exerts different and even opposite effects across the lungs simultaneously. The clinician's challenge is identifying the PEEP level that optimizes recruitment while minimizing overdistention, a necessary compromise.

Strategies

The traditional 'best compliance' strategy can fall short in determining optimal recruitment–overdistention compromise because of heterogeneity in response through the lungs: global compliance might reflect changes in recruitable regions, and less or poorly represents overdistended ones despite "optimal" compliance [2]. Novel approaches to assess recruitment and overdistention have emerged, facilitating personalized PEEP settings [3].

The recruitment-to-inflation (R/I) ratio is obtained during a single-step de-recruitment maneuver from higher to lower PEEP: the exhaled volume during the PEEP drop allows calculation of de-recruited lung units' compliance, that normalized to the compliance at low PEEP (the baby lung's compliance) yields the R/I, calculable at the bedside and providing an estimate of lung recruitability between PEEP levels (https://crec.coemv.ca/ri-ratio). Values < 0.5 indicate low recruitability [4]. Electrical impedance tomography (EIT) allows regional assessment through radiation-free thoracic impedance measurements, providing a real-time 32 × 32 pixel map of lung aeration [5]. During a decremental PEEP trial, pixel-wise compliance analysis quantifies collapse and overdistention percentages [6], allowing PEEP setting to balance these factors. Although compliance-based, this approach weighs all regions analyzed and assesses separately recruitment and overdistention, which may have different respective impacts on global compliance. Such physiology-guided

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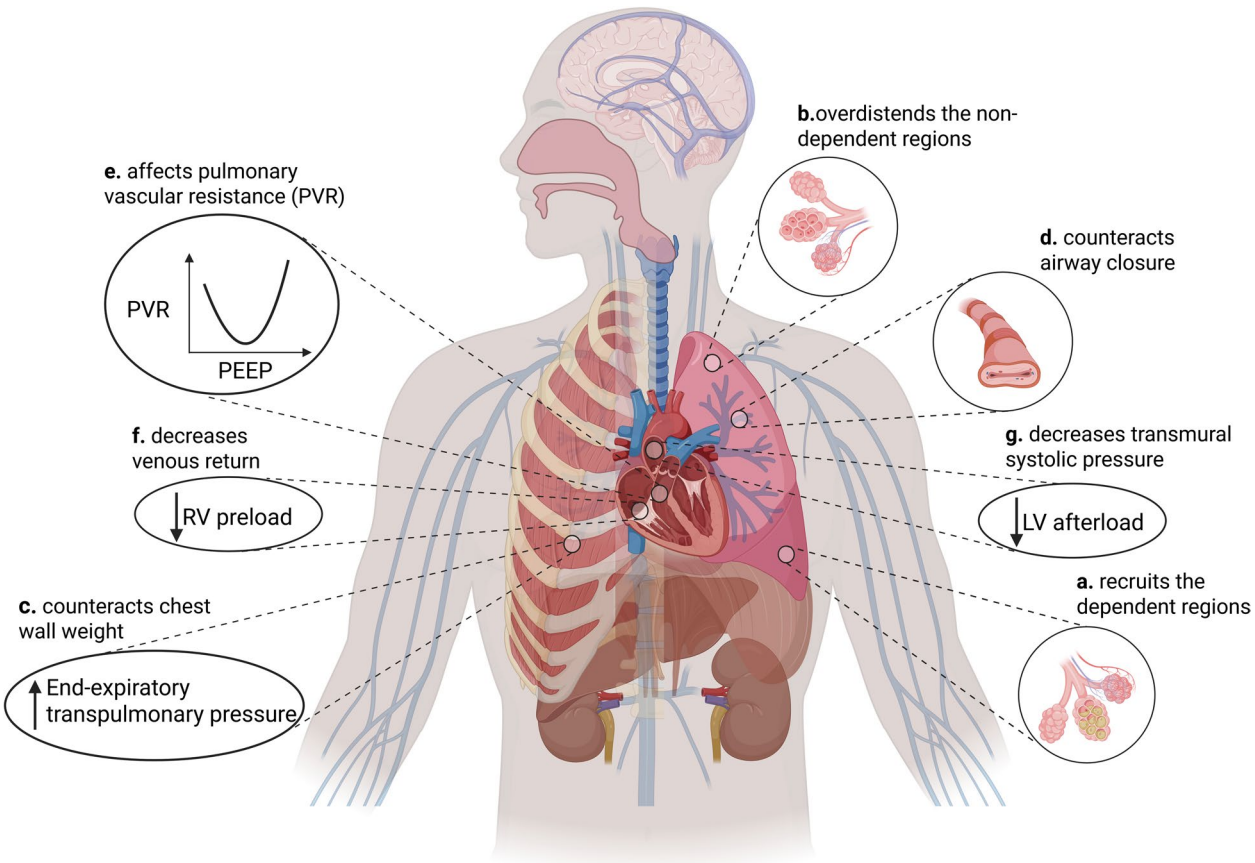

Fig. 1 The figure displays the different effects of PEEP on the lung, chest wall, and cardiovascular system. In patients with ARDS, it can reopen dependent alveoli and restore end-expiratory lung volume (**a**), but when excessive it may overinflate already ventilated units, promoting overdistention (**b**). In conditions of high chest-wall elastance, such as obesity, pneumoperitoneum, Trendelenburg positioning, or restrictive diseases, PEEP can be titrated to maintain a slightly positive end-expiratory transpulmonary pressure, avoiding dorsal collapse (**c**). In the presence of severe lung or chest-wall weight, PEEP also stabilizes small airways and avoids airway closure (**d**) by overcoming the airway-opening pressure. Cardiovascular effects on the pulmonary vascular resistance (PVR) exhibit a *U-shaped* relationship, with optimal PEEP levels reducing right-ventricular afterload (**e**). Increased intrathoracic pressure decreases venous return and right-ventricular preload (**f**), while simultaneously lowering left-ventricular afterload (**g**). Altogether, PEEP represents a systemic intervention whose optimal level balances alveolar recruitment, airway stability, hemodynamic performance, and end-organ perfusion. Created in BioRender. Menga, L. (2025) https://BioRender.com/59uck2x

ventilation was beneficial in large animal models of lung injury [7].

Load imposed by the chest wall's weight

High chest-wall load, as seen in obesity, exacerbates gravitational compression of dependent lung zones. In these cases, PEEP can be titrated using esophageal manometry to maintain a slightly positive end-expiratory transpulmonary pressure in dorsal regions, preventing collapse of dependent units (Fig. 1c). Physiological data suggest this method could be a useful titration for asymmetrical lung injury [8]. In moderate–severe ARDS, this approach has not shown mortality benefits, although a post hoc reanalysis suggested benefits in patients with lower APACHE-II scores when targeting an end-expiratory transpulmonary pressure near zero [9, 10].

Beyond the alveoli, heavy lung and chest wall—as in severe pulmonary edema, or after cardiac arrest—can compress small airways, causing airway closure during expiration and reopening during inspiration only above an airway opening pressure (AOP) (Fig. 1d) [11, 12]. This repetitive opening and closing damages the airway epithelium and increases ventilation heterogeneity with impaired gas distribution [13, 14]. The AOP represents the threshold at which effective inflation begins, and PEEP set at or above AOP stabilizes the airways, ensures uniform gas delivery, and allows accurate measurement of respiratory mechanics [14]. Regional AOP assessment

through EIT can provide a comprehensive picture in case of multiple thresholds in the lung [15].

Spontaneous breathing

PEEP influences spontaneous breathing through multiple mechanisms:

(1) Maintaining airway patency, continuous positive airway pressure, has long been utilized to prevent upper airway obstruction during sleep.
(2) Maintaining intra-thoracic airway patency, it alleviates the inspiratory load imposed by dynamic hyperinflation and intrinsic-PEEP, particularly in patients with chronic obstructive pulmonary disease. During noninvasive ventilation, PEEP becomes an essential part of the support, with higher levels required in patients with obesity hypoventilation.
(3) Although in severe asthma with bronchospasm, external PEEP may worsen dynamic hyperinflation, the effect of PEEP is difficult to predict and needs to be assessed individually.
(4) PEEP can reduce inspiratory effort in patients with hypoxemic respiratory failure when associated with better lung compliance [16].
(5) PEEP can promote active expiration, a mechanism that tends to decrease end-expiratory volume, counteracting the intended effect of PEEP. In such cases, neuromuscular blockade abolishes active expiration, improving oxygenation and increasing lung volume [17].

Cardiovascular system: pulmonary vascular resistance (PVR) and left ventricular afterload

Pulmonary vascular resistance

In ARDS, both alveolar collapse and overdistension increase PVR, explaining the *U* shape relationship between PVR and lung volume:

1. Non-ventilated regions trigger hypoxic vasoconstriction, and collapsed alveoli (behaving as West zone 4) compress intra-alveolar vessels, increasing right-ventricular (RV) afterload.
2. The increase in lung volume from excessive PEEP overinflates ventilated units, transforming them into West zone 1, where alveolar pressure exceeds capillary pressure and compresses extra-alveolar vessels. The increase in dead space also triggers hypercapnic vasoconstriction, further increasing PVR.

The relationship between PEEP and PVR is therefore *U-shaped* (Fig. 1e): if PEEP recruits without excessive overdistention, it restores normal alveolar-capillary geometry and improves ventilation/perfusion mismatch, reducing PVR (the nadir of the *U-shaped* relationship); when PEEP is excessive, PVR and RV afterload rise again [16].

Left ventricular afterload

By elevating mean intrathoracic pressure, PEEP can reduce venous return, lowering RV preload, which may exacerbate shock in severely volume-depleted patients (Fig. 1f). Clinically relevant, the rise in intrathoracic pressure decreases left ventricle (LV) transmural systolic pressure, effectively reducing LV afterload (Fig. 1g). These effects are particularly relevant during weaning, when systolic and diastolic dysfunction both contribute to spontaneous breathing trial failure. In patients with LV systolic dysfunction, the reduction in afterload alleviates myocardial stress and weaning-induced pulmonary edema [18]. Similarly, PEEP in the form of continuous positive airway pressure can support both the failing heart and lung function in cardiogenic pulmonary edema.

Conclusion

Although PEEP is clinically considered an oxygenation tool, its mechanical intrathoracic effects are much more important than the apparent effect on oxygenation: balancing recruitment and overdistention, stabilizing airways, and optimizing cardiopulmonary interactions, PEEP can protect both the lungs and the heart. Out of the scope of this short review, PEEP's effects extend beyond the thorax affecting perfusion of the brain, liver, and kidneys (Fig. 1).

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